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On June 8, 2006 the Food and Drug Administration approved the license application for the world's first vaccine against cervical and other anogenital cancers. The vaccine produces immunity to human papillomavirus, or HPV. We now have TWO vaccines that prevent cancer, the first of course being hepatitis B vaccine. This is an extraordinary advance in disease prevention, in a year with many extraordinary advances. In this segment we want to give you a brief overview of human papillomavirus, its epidemiology and disease burden, and background for the new vaccine. We will then summarize the provisional recommendations for the use of HPV vaccine which were approved at ACIP's June 2006 meeting.

Human papillomavirus is the most common sexually transmitted infection in the United States, with millions of new infections every year. Although most infections resolve spontaneously, in a small proportion of people the infection becomes chronic, and can lead to serious disease years later. We asked Dr. Mona Saraiya, a medical epidemiologist in the CDC Division of Cancer Prevention and Control, to talk about human papillomavirus, its natural history, and its relation to cancer.

Human papillomavirus, or HPV, is a complex group of DNA tumor viruses, and is the most common sexually transmitted infection in the United States. HPV infection can be completely asymptomatic and resolve spontaneously, or can persist in the infected person and lead to a variety of medical conditions. There are more than 100 different HPV types. More than 60 of these are characterized as cutaneous types and can lead to skin warts.

About 40 types infect the epithelium of the mucosa, mainly the genital mucosa. The mucosal types are further categorized as high risk types or low risk types based on their ability to cause cancer. High risk types, particularly types 16 and 18 are associated with cervical cell abnormalities, and with certain anogenital cancers. Low risk types, notably types 6 and 11, can also cause cervical cell abnormalities that usually resolve spontaneously and do not lead to cancer. Low risk types can also cause genital warts, and a rare condition called recurrent respiratory papillomatosis, a condition in which warts grow in the respiratory tract.

It is estimated that more than 6 million new infections with HPV

occur every year in the United States, and about 20 million people – 15% of the U.S. population- are currently infected. Infection with one type of HPV does not prevent infection with another type. Five to 30% of people infected with mucosal HPV are infected with multiple types of the virus. Initial HPV infection occurs soon after sexual initiation. Approximately 70% of new infections resolve spontaneously within one year, and more than 90% clear within 2 years. However, a small percentage of infections become chronic, or persistent. It is these persistent infections that can lead to serious illness years or decades later.

This graphic shows the natural history of HPV infection. The most common clinically significant manifestation of persistent genital HPV infection is cervical intra-epithelial neoplasia, or CIN. Within a few years of infection low-grade CIN called CIN 1, may develop, which may spontaneously resolve and the infection clear. Persistent HPV infection may progress directly to high-grade CIN, called CIN2 or CIN3. High-grade abnormalities are at risk of progression to cancer and so are considered cancer precursors. A small proportion of high-grade abnormalities spontaneously regress. If left undetected and untreated, years or decades later CIN2 or 3 can progress to cervical cancer. In the U.S., effective cervical cancer screening programs are able to detect disease caused by HPV early when it is usually treatable. Persistent HPV infection can lead to cervical cancer years after the initial infection.

HPV is believed to be responsible for nearly all of the 12 thousand cases of cervical cancer diagnosed each year in the United States. In addition to cervical cancer, other cancers can be attributed to HPV infection as well. This graphic shows the number of cases of select cancers in the US in 2002, and the fraction attributed to HPV types. As I mentioned earlier, among the 12,000 thousand cervical cancers, 100% are attributable to HPV. Of 3,700 anal cancers 90% are attributable to HPV. Of 4,480 vulvar or vaginal cancers and about 1,000 penile cancers, 40% are caused by HPV. Finally, among 10,000 oral and pharyngeal cancers 12% are attributable to HPV. It is clear that human papillomavirus is responsible for a large proportion of the cervical and other anogenital cancers that occur in the United States. However, although there are more than 40 different types of HPV that infect the mucosa, much of this disease burden is caused by only a few types.

This graphic shows the proportion of HPV-related disease caused by just four HPV types – 16 and 18, which are considered to be

high-risk types, and 6 and 11, considered as low-risk types. This information is important because these four HPV types are included in the new quadrivalent HPV vaccine. HPV is associated with virtually all cervical cancers, and types 16 and 18 are associated with 70% of these cancers. HPV type 16 alone is found in about half of all women with cervical cancer. High-risk HPV types 16 and 18 are also associated with 30% to 50% of high and low grade cervical abnormalities, and a proportion of anal, vulvar, vaginal and penile cancers. In addition, approximately 10% of head and neck cancers are attributed to HPV 16 and 18. Low-risk types 6 and 11 are associated with about 10% of low-grade cervical abnormalities, but 90% of genital warts, and 90% of recurrent respiratory papillomatosis.

The American Cancer Society estimates that in 2006 about 9,700 new cases of cervical cancer will be diagnosed in the United States. Approximately 3,700 women will die as a result of cervical cancer. Deaths will also occur as a result of other anogenital cancers. About 4 billion dollars will be spent this year on management of sequelae of HPV infections, primarily for the management of abnormal cervical cytology and treatment of cervical neoplasia. Disease caused by human papillomavirus is responsible for an enormous amount of suffering, death and medical cost in the United States. The burden of disease is even higher in developing countries where cervical cancer screening programs are inadequate or nonexistent. Properly used, HPV vaccine has the potential to reduce this burden of disease and save many lives, both in this country and throughout the world.

The vaccine approved by the Food and Drug Administration in June 2006 is called Gardasil, produced by Merck. The vaccine contains the outer protein, called the L1 protein, from four types of HPV – types 16 and 18, considered to be high-risk types, and types 6 and 11, considered to be low-risk types. Production of the L1 proteins uses recombinant DNA technology – similar to what is used for hepatitis B vaccine. The L1 proteins self assemble into noninfectious units, called virus like particles or VLPs. VLPs are empty protein shells without genetic material. However, they are highly immunogenic and can induce high titers of neutralizing antibody. The vaccine is supplied as a liquid in a single dose vial or syringe. The vaccine does not contain either antibiotic or preservative.

HPV vaccine is intended to prevent cancer, primarily cervical cancer. But cancer can take decades to develop following HPV infection. So a clinical trial using cancer as the outcome is not practical. Instead, other endpoints were used to determine

vaccine efficacy, such as persistent HPV infection, genital warts, and cervical intraepithelial neoplasia, or CIN, which is considered a cancer precursor. Four efficacy and safety trials were conducted that included more than 16,000 females 16 through 26 years of age. Half of these participants- more than 8 thousand women- received the vaccine. The other half received a placebo. The vaccine was found to be highly effective. This graphic shows clinical efficacy among women with no evidence of prior or current infection with vaccine HPV types. For prevention of HPV 16 or 18 related cervical intraepithelial neoplasia 2 or 3, or adenocarcinoma in situ, shown here as AIS, there were NO cases among vaccine recipients compared with 53 cases among women who received placebo, for a 100% efficacy. For prevention of ANY CIN or AIS, there were 4 cases among women who received vaccine and 83 in women who received placebo, for an efficacy of 95%. For prevention of genital warts, there was 1 case in the vaccine group and 91 cases in the placebo group, for an efficacy of 99%.

Some women enrolled in the vaccine trials had evidence of past or current infection with HPV types included in the vaccine or abnormal Pap tests. There was no evidence that the vaccine had efficacy against existing disease or infection - that is, the vaccine had no therapeutic effect. However, prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types. Female participants in the clinical trials were grouped by age. Clinical efficacy was studied in 16 through 26 year olds. Nine through 15 year olds were also enrolled to study immunogenicity and safety of the vaccine. The younger group was not followed with Pap tests. The antibody response to the vaccine among the 9 through 15 year olds was compared to the antibody response in 16 through 26 year olds in whom clinical protection was determined. This is known as immunologic bridging. It turns out that the younger participants responded to the vaccine with even higher antibody titers than the older group, so clinical protection was inferred in the younger group.

No males were included in the original immunogenicity or efficacy trials. Additional studies are in progress now, including immunogenicity studies in males and efficacy studies in females older than 26 years. Long term follow up studies are underway to look at the duration of protection. Data from these studies will be available in the next few years. Based on data from the clinical trials, HPV vaccine is approved by FDA for females 9 through 26 years of age. The vaccine is NOT approved for males of any age at this time. The routine schedule is 3

doses at 0, 2, and 6 months, similar to the schedule for hepatitis B vaccine. The minimum intervals are 4 weeks between doses 1 and 2 and 12 weeks between doses 2 and 3. HPV vaccine has been found to be safe in the clinical trials with no serious adverse events found to be associated with vaccination. The most common adverse reactions were local injection site reactions, as you would expect from an inactivated vaccine. More information about the clinical trials that led to licensure of the vaccine is available in the package insert, and will be included in the ACIP statement. Bill?

ACIP discussed HPV and HPV vaccine at several of its meetings in 2005 and 2006. They voted on recommendations for use of the vaccine at the June 2006 meeting. I will now summarize those recommendations, recognizing that they should be considered provisional until published later this year. ACIP recommends routine vaccination of females 11 or 12 years of age with the three dose series. This age corresponds to that of other recent recommendations for acellular pertussis and meningococcal conjugate vaccines. The vaccination series can be started as young as 9 years of age at the clinician’s discretion.

While the recommended age for routine vaccination is 11 or 12 years, there will be older females who could benefit from the vaccine. Vaccination is also recommended for females 13 through 26 years of age who have not been previously vaccinated. Ideally vaccine should be administered before onset of sexual activity, but females who are sexually active should still be vaccinated. In this age group, females not yet sexually active can be expected to have the full benefit of vaccination because they are not infected with HPV. Sexually active females may not have full benefit of the vaccine because they may have been already infected with vaccine HPV types. However, only a small percentage of sexually active females are likely to have been infected with all 4 HPV vaccine types. For those already infected with one or more vaccine HPV types, the vaccine would provide protection against disease caused by the other vaccine HPV types. So, although overall vaccine effectiveness would be lower when administered to a population of females who are sexually active, most females will still derive some benefit from vaccination.

There is a variety of what ACIP will call special situations for HPV vaccine. Vaccine is recommended for females 26 years of age and younger with an equivocal or abnormal Pap test, a positive HPV DNA test- meaning they are currently infected, or those with genital warts. However, these women should be informed that the

vaccine will have no effect on existing disease or infection. Women 26 years of age and younger who are lactating and breastfeeding, or who are immunocompromised may be vaccinated. However, the vaccine is NOT recommended for pregnant women.

Although HPV is an inactivated subunit vaccine ACIP prefers a conservative approach to the vaccination of pregnant women. Pregnancy testing prior to vaccination is not necessary. However, initiation of the vaccine series should be delayed until after completion of a pregnancy. If a woman is found to be pregnant after initiating the vaccination series, completion of the series should be delayed until after the pregnancy. If a vaccine dose has been administered during pregnancy, there is no indication for intervention. A vaccine in pregnancy registry has been established and women vaccinated during pregnancy should be reported. The telephone number is in the vaccine package insert.

Cervical cancer screening recommendations have not changed for females who receive HPV vaccine. HPV types in the vaccine are responsible for about 70% of cervical cancers. Females who are vaccinated could subsequently be infected with a carcinogenic HPV type not in the quadrivalent vaccine. Also, females who were sexually active prior to vaccination could have been infected with a vaccine type HPV before vaccination. Healthcare providers who are administering HPV vaccine should take the opportunity to educate women about the importance of cervical cancer screening at intervals recommended by national organizations.

Gardasil is packaged in single dose vials and syringes. It should be stored in the refrigerator with other inactivated vaccines. However, it is sensitive to light, which we usually associated with live vaccines. Be sure to keep the vials or syringes in their original boxes with the tops closed until ready for use. The vaccine should be used promptly after removal from the refrigerator.

One final note about HPV vaccine. The vaccine will be included in the Vaccines For Children program for females 9 through 18 years of age. As of August 10, 2006 a federal contract has not yet been established, which is necessary for the vaccine to actually be available through VFC. However, a contract should be established in the next few months. The availability of a vaccine to prevent human papillomavirus, and the sequelae of persistent infection is a major advance in preventive medicine. We will bring you updates on the progress of the HPV vaccination program in future editions of Immunization Update.

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